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## Neuroimaging in Functional Neurological Disorder: State of the Field and Research Agenda

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## ABSTRACT

Functional neurological disorder (FND) was of great interest to early clinical neuroscience leaders. During the 20th century, neurology and psychiatry grew apart – leaving FND a borderland condition. Fortunately, a renaissance has occurred in the last two decades, fostered by increased recognition that FND is prevalent and diagnosed using “rule-in” examination signs. The parallel use of scientific tools to bridge brain structure - function relationships has helped refine an integrated biopsychosocial framework through which to conceptualize FND. In particular, a growing number of quality neuroimaging studies using a variety of methodologies have shed light on the emerging pathophysiology of FND. This renewed scientific interest has occurred in parallel with enhanced interdisciplinary collaborations, as illustrated by new care models combining psychological and physical therapies and the creation of a new multidisciplinary FND society supporting knowledge dissemination in the field. Within this context, this article summarizes the output of the first International FND Neuroimaging Workgroup meeting, held virtually, on June 17th, 2020 to appraise the state of neuroimaging research in the field and to catalyze large-scale collaborations. We first briefly summarize neural circuit models of FND, and then detail the research approaches used to date in FND within core content areas: cohort characterization; control group considerations; task-based functional neuroimaging; resting-state networks; structural neuroimaging; biomarkers of symptom severity and risk of illness; and predictors of treatment response and prognosis. Lastly, we outline a neuroimaging-focused research agenda to elucidate the pathophysiology of FND and aid the development of novel biologically and psychologically-informed treatments.

## 1. Introduction

Functional neurological disorder (FND), also known as conversion disorder and previously termed hysteria, is a prevalent and disabling condition at the interface of neurology and psychiatry (Espay et al., 2018a; Perez et al., 2021). FND was of great interest to early clinical neuroscience leaders, with Jean-Martin Charcot stating “the neurological tree has its branches, neurasthenia, hysteria, epilepsy, all the types of mental conditions, progressive paralysis, (and) gait ataxia” (Charcot, 1887). Despite Charcot’s integrated perspective and forward-thinking “dynamic or functional lesion” theory for FND (Charcot, 1889), limitations in available neuroscientific tools at the time contributed to a

singular focus on psychological conceptualizations as originally posited by Sigmund Freud and Pierre Janet (Breuer and Freud, 1895; Janet, 1907). The divide between neurology and psychiatry expanded in the 20th century, leaving FND as a borderland condition (Fend et al., 2020). Notably, this “crisis” was met with calls for action (Edwards, 2019; Hallett, 2006; Keynejad et al., 2017; LaFrance and Devinsky, 2004; Nicholson et al., 2011).

A renaissance has occurred in the last two decades, catalyzed by emphasis on “rule-in” physical signs guiding diagnosis (Stone et al., 2010b), a growing repertoire of evidence-based treatments, establishment of a multidisciplinary FND Society ([www.fndsociety.org](http://www.fndsociety.org)), and the publication of authoritative textbooks (Hallett et al., 2016; Kozłowska et al., 2020). This renewed interest parallels recognition that FND is the 2nd most common outpatient neurologic diagnosis, with many patients remaining chronically symptomatic and incurring high healthcare costs (Gelauff et al., 2019; Stephen et al., 2021; Stone et al., 2010a). Informed by the biopsychosocial model, this sets the stage for advancing the pathophysiology of FND using multimodal neuroimaging (Baizabal-Carvallo et al., 2019; Bègue et al., 2019; Pick et al., 2019; Voon et al., 2016). Elucidating the neurocognitive mechanisms of FND will aid the identification of biomarkers guiding treatment selection and prognosis, help patients better understand their condition, decrease stigma, and promote the development of biologically and psychologically-informed treatments.

Compared to brain imaging in other neuropsychiatric disorders, FND research remains in its early stages (e.g., no samples > 100 patients, few findings replicated, and even fewer studies tied to treatments). In addition to being understudied, several inherent challenges are important considerations. Firstly, patients with FND can present with a wide range of neurological symptoms in isolation or in combination; additionally, individuals can develop different functional neurological symptoms over the natural history of their illness (McKenzie et al., 2011; Nicholson et al., 2020). Secondly, patients with FND have high rates of other physical (e.g., pain, fatigue) and psychiatric symptoms (e.g., anxiety, depression) (Goldstein et al., 2020; Kranick et al., 2011; Nicholson et al., 2020; Stone et al., 2010c). However, there is significant variability across patients. Thirdly, evidence suggests that FND has various etiologic contributors, including roles for adverse life experiences and acute/chronic physical and psychological stressors (Ludwig et al., 2018). However, risk factors vary across patients - highlighting roles for individual differences, developmental trajectories, stress-diathesis models, and gene by environment interactions

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(Apazoglou et al., 2018; Diez et al., 2020; Keynejad et al., 2019; Spagnolo et al., 2020; Voon et al., 2016). Finally, some brain areas in the neurocircuitry of FND may be at the intersection of negative affect, nociception, cognitive control, beliefs/expectations, self/emotional awareness, and developmental factors (Cretton et al., 2020; Deeley, 2016; Edwards et al., 2012; Shackman et al., 2011).

Within this context, an inaugural International FND Neuroimaging Workgroup meeting (led by D.L.P., T.R.N., S.A.) was held virtually on June 17th, 2020 to bring together FND neuroimaging researchers and thought leaders to catalyze research and collaboration in the field. This perspective article details themes discussed at the meeting. Here, we first succinctly review neural circuit models of FND based on the functional and structural neuroimaging literature. Then, we discuss the state of brain imaging research in FND emphasizing methodological considerations within core content areas: cohort characterization; control group considerations; functional neuroimaging tasks; intrinsic functional and structural brain architecture; biomarkers of symptom severity and risk of illness; and predictors and neural mechanisms of treatment response and prognosis. Lastly, we propose a neuroimaging-focused research agenda for FND to help promote high impact advances in understanding neural mechanisms and aid the development of biologically and psychologically-informed treatments.

## 2. FND Neural Circuitry - A Synopsis

Across functional and structural neuroimaging studies, evidence supports modeling FND as a multi-network brain disorder implicating alterations within and across limbic/salience, self-agency/multimodal integration, attentional, and sensorimotor circuits (Baizabal-Carvallo et al., 2019; Bègue et al., 2019; Drane et al., 2020; Foroughi et al., 2020; Szaflarski and LaFrance, 2018; Voon et al., 2016). Studies where patients engage in affectively-valenced tasks while being scanned have generally characterized increased limbic/paralimbic activity in patients with FND compared to controls (Pick et al., 2019). For example, impaired amygdala habituation and increased sensitization has been described in patients with functional motor symptoms compared to controls, along with increased functional connectivity between the amygdala and motor control circuits (Aybek et al., 2015, 2014b; Espay et al., 2018c; Hassa et al., 2017; Morris et al., 2017; Voon et al., 2010a). However, findings have been inconsistent, including reports of normal or hypoactive amygdala responses in functional movement disorder (FND-movt) and functional [psychogenic nonepileptic / dissociative] seizure (FND-seiz) cohorts, respectively (Allendorfer et al., 2019; Balachandran et al., 2020; Espay et al., 2018c). Across emotion processing and motor control tasks, altered insula, cingulate gyrus, and ventromedial prefrontal cortex activations have also been described (Aybek et al., 2015; Cojan et al., 2009; Espay et al., 2018b; Stone et al., 2007; Voon et al., 2011). These findings, particularly heightened amygdala-motor control circuit coupling, may represent markers of heightened limbic influence over motor behavior (Voon et al., 2010a). Preliminary data also suggest that baseline increased task-related corticolimbic activity may predict treatment responses to cognitive behavioral therapy (CBT) and short-term inpatient multidisciplinary motor retraining (Espay et al., 2019; Faul et al., 2020).

Task neuroimaging in FND-movt has also identified an important role for the right temporoparietal junction (rTPJ) based network in self-agency disturbances (Baizabal-Carvallo et al., 2019; Zito et al., 2020). For example, a within-group study comparing functional (involuntarily perceived) movements to volitional movements in a functional tremor cohort showed hypoactivation of the rTPJ (Voon et al., 2010b). This study also identified reduced connectivity between primary sensorimotor regions and the rTPJ, suggesting impaired feed forward processing. Other studies across a variety of FND subtypes support roles for brain circuits implicated in motor conceptualization, inhibitory control, attention, predictive processing/perceptual inference, meta-cognition, belief/expectation, emotion control, and threat-related defense

behaviors in the pathophysiology of FND (Allendorfer et al., 2019; Aybek et al., 2015; Balachandran et al., 2020; Bègue et al., 2018; Deeley et al., 2013; Edwards et al., 2012; Espay et al., 2018b; Schrag et al., 2013; Voon et al., 2016).

Resting-state functional connectivity and quantitative structural imaging approaches have been used to investigate intrinsic brain architecture in FND. In resting-state functional connectivity magnetic resonance imaging (rsfMRI) studies, FND-movt and FND-seiz cohorts have shown aberrant (generally increased) connectivity between emotion processing (cingulo-insular, amygdala) and motor control networks (Diez et al., 2019; Morris et al., 2017; van der Kruijs et al., 2012; Wegrzyk et al., 2018) compared to healthy controls; increased cingulo-insular coupling to motor control areas correlated with symptom severity in several studies (Diez et al., 2019; Li et al., 2015a, 2015b). Decreased resting-state functional connectivity between the rTPJ and primary sensorimotor regions in FND-movt compared to healthy controls has also been reported (Maurer et al., 2016); similarly, hypo-metabolism of the right inferior parietal lobule and dorsal anterior cingulate on positron emission tomography (PET) has been characterized in patients with FND-seiz (Arthuis et al., 2015). Nonetheless, only a small subset of studies combined resting-state and task-based fMRI data (Baek et al., 2017; Morris et al., 2017; Szaflarski et al., 2018), suggesting that the specific involvement of discrete brain networks in FND populations remains incompletely understood. As detailed in a recent systematic review (Bègue et al., 2019), grey matter alterations in sensorimotor, cingulo-insular and amygdala brain areas have been identified, although findings have been inconsistent (Aybek et al., 2014a; Espay et al., 2018c; Labate et al., 2012; Maurer et al., 2018; Nicholson et al., 2014; Tomic et al., 2018). The importance of individual differences and possible subgroup specific effects in understanding the pathophysiology of FND have also been demonstrated (e.g., Perez et al., 2017b) showed that reduced left anterior insula volume was only present in those patients reporting the most severe physical health impairments compared to healthy controls (Aybek et al., 2014a; Canu et al., 2020; Labate et al., 2012; Maurer et al., 2016, 2018, Perez et al., 2018b,a; Tomic et al., 2018). White matter characterization in FND is in its early stages, with initial findings pointing towards altered limbic and associative fiber bundles compared to healthy (Diez et al., 2021; Hernandez et al., 2015; Lee et al., 2015; Sojka et al., 2021; Tomic et al., 2018) and traumatic brain injury controls (Goodman et al., 2020). Developmental trajectories in pediatric FND – including the transition from adolescence to adulthood – and neurochemical (magnetic resonance spectroscopy (MRS)) studies remain markedly under-investigated (Demartini et al., 2019; Kozłowska et al., 2017a). A few imaging studies have examined the intersection of neural mechanisms and etiological (risk) factors, focusing primarily on associations between childhood maltreatment and experience-dependent neuroplasticity (Diez et al., 2020; Maurer et al., 2016, 2018; Perez et al., 2017a; Spagnolo et al., 2020). Pilot studies provide initial evidence that baseline intrinsic functional and structural profiles in FND relate to 6-month clinical outcomes (Diez et al., 2019; Perez et al., 2018b). For more details on the pathophysiology of FND, see several recent reviews (Baizabal-Carvallo et al., 2019; Bègue et al., 2019; Drane et al., 2020; McSweeney et al., 2017; Voon et al., 2016).

## 3. FND Characterization Considerations

Given phenotypic heterogeneity, interpretation of FND-related neuroimaging findings depends a great deal on rigorous cohort characterization (Gelauff et al., 2020; Matin et al., 2017; McKenzie et al., 2011). Additionally, FND presents diagnostic challenges that likely impact neuroimaging research. These reflect, in part, the somewhat underdeveloped diagnostic criteria for “Conversion Disorder (Functional Neurological Symptom Disorder)” found in the Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5) and International Classification of Diseases–11th Revision (ICD-11) (Stone et al., 2014). In DSM-5, a patient can be diagnosed with FND if they have motor and/or



sensory findings providing “evidence of incompatibility between the symptom and recognized neurological or medical conditions” (American Psychiatric Association, 2013; Stone et al., 2010b). The symptom must impair social and/or occupational functioning or lead individuals to seek a medical opinion. There are no duration or severity criteria or explicit rules for exclusion based on additional symptoms. In the neurological literature, there are also diagnostic criteria for FND subtypes, such as those for FND-seiz (LaFrance et al., 2013a) and FND-movt (Espay and Lang, 2015; Gasca-Salas and Lang, 2016; Williams et al., 1995). Unsurprisingly, varying FND diagnostic criteria have been used across studies. Despite this heterogeneity, a general emphasis on “rule-in” examination signs and semiological features guiding diagnosis has been used, including the ‘gold-standard’ adjunctive video-electroencephalography (vEEG) for FND-seiz (LaFrance et al., 2013a).

Despite these potential concerns with the current criteria, FND diagnoses are reliable over time - misdiagnosis is rare in published studies (Stone et al., 2005). The same cohort studies in adults also show symptom persistence in the majority, indicating that we are generally not dealing with transient symptoms, at least in research populations where participants have usually been ill for months to years before inclusion (Gelauff and Stone, 2016).

Based on phenotypic complexity, FND neuroimaging researchers need to consider how the following factors could lead to heterogeneity:

- a. *Symptom severity*: For example, we likely want to differentially consider a patient with a heavy leg that drags occasionally and someone with quadriplegia.
- b. *Episodic vs. persistent*: Whilst some symptoms are episodic such as seizures, others may vary. Patients may at times have only intermittent limb weakness, and at other instances a more static paralysis.
- c. *Duration and Onset*: It is likely that someone who has had functional paraplegia for 20 years would have different neuroimaging correlates compared to an individual with symptoms for a month (including compensatory neuroplasticity changes from underuse) (Newbold et al., 2020). Illness duration may be especially important in connectivity and structural neuroimaging studies. Additionally, FND neural mechanisms in children/adolescents, adults and late-life presentations require inquiry regarding to what extent mechanisms are shared across the lifespan.
- d. *Symptom type and overlap*: Many patients with FND have overlapping symptoms. For example, some with functional tremor or dystonia will also exhibit functional weakness or sensory deficits in the same limb and/or have current or past FND-seiz (Gelauff et al., 2020; Matin et al., 2017).
- e. *Symptom location*: It may be important for some studies to explicitly define symptom location, for example, face, arm or leg, and the laterality.

Additional physical and mental health diagnoses in FND, at least as currently defined, are the norm rather than an exception (Nicholson et al., 2020). Pain, fatigue, insomnia, and cognitive symptoms are generally found in more patients with FND than not. Other functional somatic disorders such as functional bowel, bladder and cardiorespiratory symptoms are also common. Psychiatric conditions, especially affective, trauma-related and/or dissociative disorders, are typically present in over 50% of most FND samples, with lifetime rates even higher (Bowman and Markand, 1996; Goldstein et al., 2020; Gray et al., 2020; Kozłowska et al., 2011; Kranick et al., 2011; Sar et al., 2004; Stone et al., 2010c). Personality disorders also exist in patients with FND at higher frequencies than that in the general population, with personality traits such as neuroticism, obsessiveness and/or emotional dysregulation commonly recognized (Ekanayake et al., 2017; Szaflarski et al., 2015). Adverse life events, a predisposing vulnerability for FND, are frequently reported though not universally so (Ludwig et al., 2018). Additionally, other neurological conditions may be present, such as patients with both FND-seiz and epileptic seizures, or individuals with

Parkinson's disease and motor FND (Kutlubaev et al., 2018; Wissel et al., 2018); the intersection of mild traumatic brain injury and FND-seiz is also well recognized (LaFrance et al., 2013b; Popkirov et al., 2018). Psychotropic medications are frequently prescribed in patients with FND to manage anxiety, depression, pain, fatigue, and insomnia, among other symptoms. In FND, neuroimaging studies have varied in their characterization of other concurrently present medical/neurological and psychiatric conditions; for example, only a subset of studies performed structured psychiatric interviews. Additionally, only a few studies have attempted to adjust for psychiatric symptoms and medication effects in their analyses. Relatedly, serotonergic-based medications modulate emotion processing circuits (particularly the amygdala), and efforts to adjust for medication use may help reconcile differences in findings across studies (Godlewska et al., 2012).

How is the neuroimaging researcher to deal with this complexity and potential confounding? Control group considerations discussed below are one approach. Studying FND severity using within-group designs may also be helpful but complex, as studies show that symptom severity and affective symptoms can co-vary (Rawlings et al., 2017). Additionally, there are difficulties in knowing whether to attempt objective measurements or to rely entirely on patient reports. A recent international collaboration on FND outcome measures concluded that measures based on subjective reports were probably more meaningful, especially when considering that symptoms like functional leg weakness, by definition, can often be demonstrated temporarily to be absent (Nicholson et al., 2020; Pick et al., 2020). Similarly, regarding risk factors, subjective reports of high childhood maltreatment burden are strong predictors of later-life psychopathology - irrespective of objective documentation (Danese and Widom, 2020). Although large samples are required to avoid type 2 errors, another solution includes using statistical adjustments for possible confounding factors in secondary analyses (e.g., performing analyses and reporting findings adjusting and not adjusting for variables such as depression scores). A more radical perspective is to reframe some of the diagnostic and comorbidity challenges by adopting a position that FND, in its naturally presenting state, is not a pure disorder, and its ‘comorbidities’ are intrinsic to its pathophysiology. Those seeking to study FND should therefore potentially not regard prevalent ‘comorbidities’ as noise / nuisance factors, but part of the condition to be understood.

#### 4. Control Group Considerations

The choice of controls is a key design element for FND studies. In FND, the majority of studies to date have used healthy controls or within-subject designs (Allendorfer et al., 2019; Bègue et al., 2019; McSweeney et al., 2017; Voon et al., 2016). Using healthy controls has benefits, including that between-group findings can be established to be outside the normal range; however, covarying affective symptoms and psychotropic medication use in the FND cohort limit the ability to relate observations as definitively associated with FND itself.

Another option is to use patient controls with comparable non-FND symptoms to those found in the FND cohort. Only a few studies have used neurological or psychiatric controls in FND research to date, including primary dystonia (Espay et al., 2018b; Schrag et al., 2013), essential tremor (Espay et al., 2018c), traumatic brain injury (Balachandran et al., 2020; Goodman et al., 2020) and a mixed depression/anxiety psychiatric control group (Diez et al., 2020). However, neurological and psychiatric control groups are inherently abnormal, and therefore attributing findings solely to the FND group can be challenging. Including two controls groups (one healthy and one neuropsychiatric control group) may be preferable for many study designs (Espay et al., 2018b, 2018c; Szaflarski et al., 2018); it may be particularly useful when the choice of the neuropsychiatric control group enables the subtraction out of effects related to conditions commonly co-occurring in FND (e.g., chronic migraine, generalized anxiety disorder, personality disorder, etc.), while the parallel use of healthy controls

**Table 1**

Examples of task-based neuroimaging studies in functional neurological disorder.

Tasks	Task Descriptions	Construct(s) Interrogated	FND Type	FND Studies
Motor-related	Preparing and attempting to move limbs	Motor preparation, performance, observation, control, and/or imagery	FND-par	Marshall et al., 1997
	Joystick paced movements		FND-par	Spence et al., 2000
	Preparing and attempting projected hand movements		FND-par	Burgmer et al., 2006
	Action choice based on visual stimuli		FND-par	Stone et al., 2007
	Judging laterality of visually presented rotated hands		FND-par	de Lange et al., 2007
	Go / No-Go task		FND-par	Cojan et al., 2009
	Imagination and execution of movements		FND-par	van Beilen et al., 2011
	Action selection task		FND-movt	Voon et al., 2011
	Metronome paced movements		FND-dystonia	Schrag et al., 2013
	Passive movements of hands		FND-par	Hassa et al., 2017
	Finger tapping task		FND-dystonia	Espay et al., 2018b
	Finger tapping task		FND-tremor	Espay et al., 2018c
Affective and threat processing	Facial emotion recognition	Affective processing & control, traumatic memory processing, avoidance learning, and/or psychological stress response	FND-movt	Voon et al., 2010a
			Motor FND	Aybek et al., 2015
			FND-par	Hassa et al., 2017
			FND-dystonia	Espay et al., 2018b
			FND-seiz	Szaflarski et al., 2018
			FND-tremor	Espay et al., 2018c
			FND-tremor	Espay et al., 2019
			FND-dystonia	Espay et al., 2018b
			FND-tremor	Espay et al., 2018c
			FND-tremor	Espay et al., 2019
			FND-movt	Sojka et al., 2019
			Motor FND	Aybek et al., 2014b
Self-agency & motor awareness	Viewing emotive images		FND-mixed	Morris et al., 2017
			FND-seiz	Allendorfer et al., 2019
Emotion-motor interaction	Recall of trauma-themed events with varying relevance to symptom onset	Affectively conditioned associative learning		
Somatosensory perception	Easy vs. hard math and positive vs. negative social feedback (Montreal Stress Imaging Task)			
Other paradigms	Imaging Task)			

*Note:* task organization in this table aims to broadly group paradigms across studies based on similar constructs tested, however, the reader should note that there are important nuances to many of these tasks that should be carefully inspected by reading the original article. Abbreviations: FND, functional neurological disorder; FND-seiz, functional [psychogenic nonepileptic / dissociative] seizures; FND-dystonia, functional dystonia; FND-tremor, functional tremor; FND-mixed, FND with mixed symptoms; FND-par, functional limb weakness/paresis; FND-movt, functional movement disorder; motor FND includes both FND-movt and FND-par; FND-3PD, persistent postural perceptual dizziness; FND-sensory, FND with sensory symptoms; TBI, traumatic brain injury.

contextualize findings as outside or inside the range of normal. While a transdiagnostic approach embracing the recruitment of mixed FND cohorts is increasingly being adopted to aid the investigation of shared neural mechanisms across subpopulations (Perez et al., 2015), including two or more isolated FND subtypes (e.g., functional limb weakness vs. functional dystonia) may aid the identification of subtype-specific findings (Canu et al., 2020; Sojka et al., 2021; Tomic et al., 2018). Relatedly, initial machine learning neuroimaging studies investigating the utility of such approaches as adjunctive diagnostic tools used healthy controls (Vasta et al., 2018; Wegrzyk et al., 2018), but including

conditions on the differential diagnosis for FND (e.g., epilepsy, primary dystonia) will further test the specificity of such methods.

In terms of state (patients with active symptoms) vs. trait (patient-specific characteristics in those without current symptoms), within-group longitudinal designs can be informative. Some studies used patients as their own controls, with and without symptoms (Vuilleumier et al., 2001) or before and after treatment (Espay et al., 2019; Faul et al., 2020). An advantage of within-subject designs are their enhanced statistical power.

## 5. Task-based Neuroimaging

Task-based functional MRI (fMRI) measuring blood-oxygen-level-dependent (BOLD) signal, and to a lesser extent nuclear imaging approaches (i.e., positron emission tomography (PET), single-photon emission computed tomography (SPECT)) has been used to interrogate neural activations in FND. Examples of experimental paradigms used to date are illustrated below and in Table 1.

Initial studies explored motor execution/control circuits in patients with functional limb weakness while participants tried to move their paretic limb compared with their unaffected limb (Marshall et al., 1997), or compared with subjects feigning limb paralysis (Spence et al., 2000; Stone et al., 2007). Other early functional limb weakness case studies probed motor preparedness, motor observation and imagined movements (Burgmer et al., 2006; Cojan et al., 2009; de Lange et al., 2007; Marshall et al., 1997; van Beilen et al., 2011). Basic motor performance (e.g., finger tapping) tasks have also been used in FND-movt populations (Espay et al., 2018b, 2018c; Schrag et al., 2013). Recent studies have investigated the interplay between motor control and emotion processing using paradigms such as an emotional Go/No-Go (Faul et al., 2020; Hassa et al., 2017); in another study, participants were asked to maintain grip strength while viewing affectively-valenced images (Blakemore et al., 2016).

Limbic and salience networks can be interrogated with affectively-valenced facial expression processing tasks, an approach commonly used in FND research (Aybek et al., 2015; Hassa et al., 2017; Voon et al., 2010a). Other studies used affectively-valenced picture viewing tasks (e.g., the International Affective Picture System) to probe emotion processing/regulation circuits in FND populations (Espay et al., 2018b, 2018c; Sojka et al., 2019). Using a different approach, an affective memory response was explored by invoking traumatic memories with varying theorized relevance to patients' functional neurological symptoms in the scanner (Aybek et al., 2014b; Kanaan et al., 2007). Cognitive-mediated stress responses in FND have also been investigated using easy vs. hard mathematical calculations and positive vs. negative social stressors from the Montreal Stress Imaging Task (Allendorfer et al., 2019; Balachandran et al., 2020).

Another construct explored is impaired self-agency in patients with FND-movt perceiving their functional movements as involuntary (Bai-zabal-Carvallo et al., 2019). One study compared brain activations during two conditions where the voluntary perception of tremor was different: in one condition patients could voluntarily trigger a tremor by moving their arm into a certain position and in the other condition patients displayed their functional tremor without any perceived voluntary control (Voon et al., 2010b). Other studies have interrogated self-agency using the Libet clock paradigm (Baek et al., 2017) and by manipulating visual feedback of a motor action with a cyber glove (Nahab et al., 2017).

Additional constructs probed in FND task-based neuroimaging research to date include avoidance learning (Morris et al., 2017), motor inhibition (Cojan et al., 2009), virtual-reality associated motion perception (Riccelli et al., 2017), meta-cognition (Bègue et al., 2018), symptom modeling with suggestion (Deeley, 2016), somatosensory processing (Burke et al., 2014; Ghaffar et al., 2006; Vuilleumier et al., 2001) and nociception (Mailis-Gagnon et al., 2003). No functional neuroimaging studies to date have explicitly probed catastrophizing, interoception or predictive processing more broadly, which are additional constructs of theoretical relevance to the pathophysiology of FND (Drane et al., 2020; Edwards et al., 2012; Fobian et al., 2020; Koreki et al., 2020). Relationships between lateralized symptoms and hemispheric brain activations also require additional inquiry, including the use of flipped and unflipped data analytic approaches (van Beilen et al., 2011).

For task-based neuroimaging, there are several relevant methodological considerations. Block designs favored in many early FND studies have superior statistical power but can yield confounds arising from

stimulus order predictability (Friston et al., 1999). Event-related designs, while lacking somewhat in statistical power, allow sorting of trial responses according to specific behavioral outcomes such as motor errors or a subjective judgment of affectively-valenced stimuli (Chee et al., 2003). Although task fMRI has good spatial resolution (compared to PET and SPECT), temporal resolution is limited by the hemodynamic response, which is a concern when studying sub-second range cognitive-affective-perceptual processes (Khanna et al., 2015). Task fMRI techniques in-development utilizing fast, sub-second approaches may soon overcome these issues (Sahib et al., 2018).

## 6. Resting State Networks

rsfMRI measures BOLD signal while an individual is awake but not engaged in any specified task. To analyze BOLD signal in the resting-state, some FND researchers have studied the temporal dynamics of the time series (e.g., amplitude of low frequency fluctuations (ALFF)) (Li et al., 2015a; Yang et al., 2020). However, rsfMRI approaches interrogating brain networks in FND cohorts are more popular (Chen et al., 2020; Foroughi et al., 2020) (see Table 2). rsfMRI analyses examine the dependency between the time series of different brain regions to compute a similarity measure between them. A common connectivity measure used in FND research is seed-based functional connectivity that characterizes relationships between a seed (region-of-interest (ROI)) and the rest of the brain. In FND studies, seed selection has been based on task fMRI activations within the same cohort (Allendorfer et al., 2019; Baek et al., 2017; Szaflarski et al., 2018; van der Kruijs et al., 2012), neuroanatomical atlases (e.g., automatic anatomic labeling) (Canu et al., 2020; Lee et al., 2018; Li et al., 2015b; Morris et al., 2017), voxel-based coordinates informed by meta-analyses (Canu et al., 2020; Maurer et al., 2016), or *a priori* hypotheses (Spagnolo et al., 2020). While seed-based connectivity is readily interpretable, this approach does not necessarily capture a complete picture of the global brain architecture. To reduce the dimensionality of whole brain data into a set of networks, studies in FND have employed data-driven parcellations including independent component analysis (ICA) (Canu et al., 2020; van der Kruijs et al., 2014) and clustering (Monsa et al., 2018). To study intrinsic network architecture properties, graph theory rsfMRI techniques have been used, including characterizing network segregation and integration (Rubinov and Sporns, 2010). Here, nodes (ROIs) and the connectivity parameter (known as an edge or link) must be defined. Connectivity is represented by an adjacency matrix (either voxel  $\times$  voxel or ROI  $\times$  ROI) that examines the relationships across all pairs of regions. Several FND studies have applied graph theory rsfMRI, using connectome measurements including weighted-degree (centrality), clustering coefficient, small worldness, and link-level metrics (Amiri et al., 2021; Diez et al., 2020; Ding et al., 2013, 2014). For interpretability, nodes that are highly connected to other brain areas (indexed via centrality) are termed "hubs". A hybrid seed-based graph theory approach that allows for the characterization of information flow across brain networks, stepwise functional connectivity, has also been used in one study (Diez et al., 2019). Dynamic rsfMRI (e.g., sliding window approaches) characterize the intrinsic variance of network connectivity across the duration of the scan (rather than averaging BOLD signal for the entire scan); one FND study has used this methodology to date (Marapin et al., 2020). Lastly, while the above techniques extract network properties and subsequently perform statistical analyses, machine learning can identify features with potential diagnostic utility; a linear Support Vector Machine classifier was used in an FND cohort to identify network features with predictive diagnostic potential (Khosla et al., 2019; Wegrzyk et al., 2018).

Additionally, while the full range of rsfMRI methodological considerations is beyond the scope of this article, head motion is a noteworthy issue given the presence of motor symptoms; as such, preprocessing and statistical analyses should explicitly address head motion artifacts (Power et al., 2015). Several studies have included head

**Table 2**

Resting-state fMRI approaches performed in functional neurological disorder to date.

Technique	Methodological Description	Strengths & Weaknesses	FND Studies
Amplitude of Low Frequency Fluctuations (ALFF)/Fractional ALFF (fALFF)	Frequency-domain analyses based on power spectrum reflecting spontaneous regional neural activity.	ALFF has better reliability in grey matter than fALFF. ALFF is more sensitive to individual differences, while fALFF may be more prone to bias from physiological noise.	Li et al., 2015a; Maurer et al., 2016; Spagnolo et al., 2020
Seed-Based rsfMRI	Evaluates correlations between time series in a given seed (ROI) compared to other brain areas to identify spatially distinct networks.	Readily interpretable. Findings are dependent in part on seed selection. Approaches to seed selection include using anatomical atlases, coordinates informed by the literature (e.g., meta-analysis) or task-based activations among other possibilities.	Allendorfer et al., 2019; Baek et al., 2017; Canu et al., 2020; Lee et al., 2018; Li et al., 2015a,b; Maurer et al., 2016; Morris et al., 2017; Spagnolo et al., 2020; Szaflarski et al., 2018; van der Kruijs et al., 2012
Data-Driven Component and Clustering Approaches	Analyses aim to reduce the dimensionality of whole brain data into a smaller set of networks, using approaches such as independent component analyses (ICA) and clustering analysis.	Techniques are model free and not dependent on seed selection. In ICA, user pre-specifies or estimates the number of components. Once voxels are grouped together, the user discerns which data sets reflect neural organization and which reflect physiological noise.	van der Kruijs et al., 2014; Monsa et al., 2018; Canu et al., 2020
Graph Theory Network Applications	Characterize the functional connectome using a correlation matrix and defining the nodes (ROIs) and connectivity strength measurements (links or edges).	Allows for the study of both of specific networks (segregation) as well as interactions across networks (integration). Techniques to define nodes include use of anatomical atlases and voxel-based approaches. Procedures are computationally demanding and multiple comparison considerations are important. Clinical translation of certain graph theory network properties to brain networks can be challenging.	Amiri et al., 2021; Diez et al., 2019, 2020, Ding et al., 2013, 2014
Dynamic (Sliding Window) rsfMRI	Characterizes the intrinsic variance of network connectivity across the duration of the resting-state scan (rather than averaging BOLD signal for the entire scan)	Allows for the quantification of fluctuations in resting-state connectivity across the duration of the scan. Window length selection is somewhat arbitrary and approach can be sensitive to outliers.	Marapin et al., 2020
Machine Learning	Analyses aim to distinguish a given patient group from comparison cohorts. Predictions can also be applied to characterizing relationships between non-imaging measures of interest and individual differences.	In unsupervised approaches, mathematical computations seek to disentangle explanatory variables in rich, unlabeled rsfMRI data. Other approaches are supervised with greater user input regarding criteria for classification. For classifier-based analyses, the specificity and sensitivity of the findings can be calculated. Computations generally require large sample sizes and similar to graph theory, this approach is computationally demanding.	Wegrzyk et al., 2018

*The Abbreviations:* FND, functional neurological disorder; BOLD, blood-oxygen-level-dependent; rsfMRI, resting-state functional connectivity magnetic resonance imaging; fMRI, functional magnetic resonance imaging; ROI, region of interest.

motion parameters as nuisance variables, as well as performing spike-detection (scrubbing) to “de-noise” data (Allendorfer et al., 2019; Diez et al., 2020, 2019a; Lee et al., 2018; Maurer et al., 2016; Spagnolo et al., 2020; Szaflarski et al., 2018).

## 7. Grey Matter Characterization

Given that brain structure–function relationships are closely coupled, a growing body of literature characterized grey matter in patients with FND. To date, these approaches include manual tracing (Atmaca et al., 2006, 2016), voxel-based morphometry (VBM) (Aybek et al., 2014a; Espay et al., 2018c; Kozłowska et al., 2017a; Labate et al., 2012; Maurer et al., 2018; Perez et al., 2017a, 2017b, 2018b; Riederer et al., 2017) and surface-based methods (Labate et al., 2012; Nicholson et al., 2014; Nigro et al., 2019; Ospina et al., 2019; Perez et al., 2018a; Ristic et al., 2015; Tomic et al., 2018; Vasta et al., 2018; Williams et al., 2018) (see Table 3). Manual tracing, historically considered the gold standard, requires a skilled neuroanatomist to hand trace ROIs. This is a time- and resource-intensive process, with variable intra- and inter-operator reliability (Morey et al., 2009). However, manual tracing can provide a good solution to quantifying volumes in relatively discrete subcortical structures. In FND, studies have used manual tracing to quantify basal ganglia, thalamic and pituitary volumes (Atmaca et al., 2006, 2016).

In FND research, manual tracing has been largely replaced by automatic methods such as VBM and surface-based morphometry. VBM is a fully-automated process that statistically analyzes each T1 anatomical scan at the voxel-level. This procedure requires that images be transformed to a common anatomical space to assure correspondence across subjects, generally using the Statistical Parametric Mapping (SPM) (Ashburner and Friston, 2000) or FMRIB Software Library (FSL) VBM analysis pipelines (Jenkinson et al., 2012). Other important VBM steps include tissue segmentation, where normalized images are separated into grey matter, white matter and cerebrospinal fluid components using tissue probability masks, and smoothing, where data is made more compatible with the Gaussian field model. Some processing steps can introduce variability in statistical analyses, such as co-registration and partial-volume effect concerns (Larvie and Fischl, 2016). Several studies in FND have employed VBM to perform whole-brain (Aybek et al., 2014a; Espay et al., 2018c; Kozłowska et al., 2017a; Labate et al., 2012; Maurer et al., 2018; Perez et al., 2017b) or ROI-based analyses (Nicholson et al., 2014; Perez et al., 2017a, 2018b). Additionally, while surface-based analyses have been more widely used for cortical thickness measurements, one FND study combined VBM and voxel-based cortical thickness analyses (Aybek et al., 2014a).

Surface-based, semi-automated algorithms implemented in tools like *FreeSurfer* (<http://surfer.nmr.mgh.harvard.edu/fswiki>) enable the quantification of grey matter architecture based on reconstructed grey



matter, white matter and pial surface boundaries (Fischl, 2012). Vertex measurements from these surfaces enable the calculation of several morphometric determinations, including cortical thickness, surface area, and curvature. Automated tracings using *FreeSurfer* also allow segmentation of subcortical structures, enabling volume measurements. While *in vivo* surface-based calculations have been validated against post-mortem measurements (Rosas et al., 2002), visual inspection of segmentation results is required to ensure that surface determinations were accurately demarcated. In the FND literature, whole-brain cortical surface analyses have been commonly employed (Labate et al., 2012; McSweeney et al., 2018; Nigro et al., 2019; Ospina et al., 2019; Perez et al., 2018a; Ristic et al., 2015; Tomic et al., 2018; Vasta et al., 2018; Williams et al., 2018), with cortical thickness measures extracted in all studies. Additionally, one study combined surface-based measurements with a random forest machine-learning algorithm to investigate structural MRI characteristics that distinguished patients with FND-seiz compared to healthy controls (Vasta et al., 2018). Other multivariate analyses such as source-based morphometry have yet to be used in patients with FND.

Grey matter characterization using neuroimaging techniques also has general limitations that are important considerations, such as insufficient contrast in T1-weighted sequences to completely delineate deep grey matter structures (Pagnozzi et al., 2019). False positive rates may also be higher for volume and surface area calculations compared to cortical thickness measurements (Greve and Fischl, 2018).

## 8. White Matter Characterization

White matter characterization using diffusion-weighted imaging in FND is in its early stages. Diffusion-weighted imaging, commonly diffusion tensor imaging (DTI), quantifies the movement of water molecules along axons and allows for an *in vivo* characterization of a) the local microstructural white matter integrity, and b) the reconstruction of white matter connections using tractography (Jones et al., 2013). Tractography-based graph theory analyses may further elucidate structural brain networks (Rubinov and Sporns, 2010).

Voxel-based approaches to characterize white matter in patients with FND rely on scalars derived from DTI, most commonly fractional anisotropy (FA, a measure of microstructural integrity) and mean diffusivity (MD). These have been investigated in FND cohorts using tract-based spatial statistics (TBSS, i.e. voxel-wise analysis of skeletonized local diffusion measures) (Jungilligens et al., 2021; Lee et al., 2015;

Sone et al., 2019; Tomic et al., 2018) and voxel-based analysis (Sojka et al., 2021). Alternatively, individual white matter tracts or a whole-brain connectome can be constructed using tractography. FND studies have applied both deterministic (Ding et al., 2013; Hernando et al., 2015; Li et al., 2015b) and probabilistic tractography (Diez et al., 2021; Jungilligens et al., 2021; Sojka et al., 2021). Furthermore, three of the aforementioned studies (Diez et al., 2021; Ding et al., 2013; Sone et al., 2019) used graph theoretical analysis to study the structural connectome of patients with FND. One study employed network lesion mapping to identify the grey matter origins of white matter findings (Sojka et al., 2021). In addition to conventional diffusion-weighted imaging, high angular resolution diffusion imaging (HARDI), which can more accurately delineate crossing fibers, has been applied in a FND-seiz cohort; this study also used the neurite orientation dispersion and density indices (NODDI) toolbox to characterize neurite dispersion, density and isotropic-free water volume fraction (Goodman et al., 2020). See Table 4 for a description of white matter approaches published in FND to date.

While diffusion-weighted imaging is a valuable tool, there are methodological considerations. Due to its reliance on detecting small displacements of water, DTI is susceptible to head motion artifacts (Yendiki et al., 2014). Furthermore, conventional DTI measures only one overall direction and degree of isotropy per voxel. In voxels containing crossing fibers, this leads to difficulties in estimating the underlying ‘true’ diffusion directions contributing to the overall signal. Approaches such as HARDI may more reliably account for crossing fibers, but acquisition times are longer than conventional DTI (Schilling et al., 2018).

## 9. Other Imaging Approaches

Besides functional/structural MRI and diffusion-weighted techniques, other neuroimaging modalities used in FND research include nuclear medicine (i.e., PET and SPECT), magnetic resonance spectroscopy (MRS) and near-infrared spectroscopy (NIRS). Nuclear medicine approaches have been applied to FND populations during both rest and task performance (Czarnecki et al., 2011; Galli et al., 2019; Marshall et al., 1997; Schrag et al., 2013; Song et al., 2014; Spence et al., 2000; Vuilleumier et al., 2001). Interictal and ictal SPECT, and interictal PET, have been used to differentiate FND-seiz and epileptic seizure cohorts (Baslet et al., 2021; Biraben et al., 1999; Neiman et al., 2009; Olver et al., 2019; Varma et al., 1996).

**Table 3**

Grey matter characterization approaches performed in functional neurological disorder to date.

Technique	Methodological Description	Strengths & Weaknesses	FND Studies
Manual tracing	Quantification of grey matter structures based on tracings by hand of the whole brain or regions-of-interest.	Historically considered the gold standard as it provides accurate identification of neural structures, and is particularly useful for small subcortical and limbic structures. Time- and resource-demanding process not readily applicable to large datasets.	Atmaca et al., 2006, 2016
Voxel-based morphometry (VBM)	Statistical comparison of grey-matter intensities for each voxel between participants.	Fully automated process that can be applied to large datasets to quantify voxel-level grey matter density. Several processing steps may be prone to variability, including co-registration and partial-volume effect concerns.	Aybek et al., 2014a; Espay et al., 2018c; Kozłowska et al., 2017a; Labate et al., 2012; Maurer et al., 2018; Perez et al., 2017a,b, 2018b; Riederer et al., 2018
Surface-based morphometry	Reconstruction of the surfaces between grey matter, white matter and pial surface, allowing for the calculation of cortical metrics (thickness, surface area, curvature etc.)	Semi-automated process that can be applied to large datasets, with <i>in vivo</i> measurements correlating well with post-mortem measurements. Provides a volume-based segmentation stream for subcortical structures. Pial and white matter boundaries benefit from visual inspection and some metrics may be difficult to interpret (e.g., curvature).	Labate et al., 2012; McSweeney et al., 2018; Nicholson et al., 2014; Nigro et al., 2019; Ospina et al., 2019; Perez et al., 2018a; Ristic et al., 2015; Tomic et al., 2018; Vasta et al., 2018; Williams et al., 2018

The Abbreviations: FND, functional neurological disorder.

In terms of neurochemical studies, two MRS studies have been performed in FND (Demartini et al., 2019; Simani et al., 2020). A NIRS study differentiated cardiogenic syncope from functional episodes during a tilt-test examination (Claffey et al., 2020), as it confirmed a stable cerebral tissue saturation index. While beyond the scope of this article, electrophysiological approaches including quantitative electroencephalography (EEG), spectral power, source localization, and event-related potentials have also been applied to FND (Barzegaran et al., 2015; Hallett, 2016a, 2016b; Kozłowska et al., 2017b, 2018; Meppelink et al., 2017; van der Salm et al., 2012). Promising techniques not yet used to study the pathophysiology of FND include ligand-based nuclear medicine techniques (including MRI-PET approaches), EEG-fMRI, and combined transcranial modulation-fMRI studies.

## 10. Individual Differences: Biomarkers of Symptom Severity, Illness Duration and Risk Factors for Developing FND

There is a small but growing number of studies reporting on the neural correlates of symptom severity and illness duration as well as variables that might influence risk of developing FND, particularly adverse childhood experiences. Across structural and functional neuroimaging studies, indices of patient-reported symptom severity (e.g., FND-seiz frequency, disability from functional dizziness) and/or illness duration have been used as covariates of interest in within-group designs in several FND cohorts (Atmaca et al., 2016; Aybek et al., 2014a; Diez et al., 2019, 2021; Jungilligens et al., 2021; Kozłowska et al., 2017a; Labate et al., 2012; Lee et al., 2015; Li et al., 2015a,b; Maurer et al., 2018; McSweeney et al., 2018; Nicholson et al., 2014; Perez et al., 2017a; Riccelli et al., 2017).

Data on brain – risk factor relationships in FND are relatively sparse, and mostly inferred from trauma history. Notably, several studies have investigated brain – trauma burden relationships using self-report

measures (e.g., Childhood Trauma Questionnaire, Life Events Checklist) in FND cohorts (Diez et al., 2020; Jungilligens et al., 2021; Kozłowska et al., 2017a; Maurer et al., 2016, 2018; Perez et al., 2017a; Spagnolo et al., 2020). The role of other biopsychosocial-informed risk factors such as dissociation, alexithymia, personality profiles, insecure attachment, and social behaviors have received minimal attention to date (Labate et al., 2012; Ospina et al., 2019; Passamonti et al., 2018; Perez et al., 2018a; Sojka et al., 2019; van der Kruijs et al., 2012, 2014; Williams et al., 2018). Furthermore, in some patients dissociation and alexithymia may represent intrinsic aspects of the same FND-related pathophysiology rather than risk factors per se. Sex-differences in the neurobiology of FND are also understudied (Maurer et al., 2018; Perez et al., 2017a; Williams et al., 2018).

Given the clinical heterogeneity found in FND, potential biological subtypes (e.g., intermediate phenotypes and endophenotypes) may be important considerations. For example, individual differences in childhood abuse burden correlated with corticolimbic resting-state functional connectivity in FND cohorts (Diez et al., 2020; Maurer et al., 2016); this suggests that a subset of individuals with FND (particularly those with adult onset) could potentially be conceptualized as having a delayed trauma-related disorder. Furthermore, differences in single-nucleotide polymorphisms of the tryptophan hydroxylase 2 gene in the context of studying gene by environment interactions have preliminarily identified biologically distinct FND subgroups (Spagnolo et al., 2020).

## 11. Imaging Predictive Biomarkers and Mechanisms of Treatment Response

With interest in developing FND treatments, recognized heterogeneity in outcomes among patients, and challenges in defining optimal clinical trial outcome measures (Nicholson et al., 2020; Pick et al., 2020), neuroimaging may help elucidate neural mechanisms and

**Table 4**

White matter characterization approaches performed in functional neurological disorder to date.

Technique	Methodological Description	Strengths & Weaknesses	FND Studies
Tract-based spatial statistics (TBSS)	Voxel-wise analysis of diffusion indices to quantify the local strengths of axonal directionality within white matter tracts.	Assesses white matter microstructural integrity, independent of local fiber orientation. Results are difficult to interpret in areas of crossing fibers, subject to partial volume effects in thin tracts and prone to head movement effects.	Jungilligens et al., 2021; Lee et al., 2015; Sone et al., 2019; Tomic et al., 2018
Voxel-based analysis (VBA)	Voxel-wise approach to quantify diffusion indices throughout the subcortical white matter.	White matter assessments are not limited to a skeletonized map. If used in isolation, some difficulty relating findings to known fiber bundles. Accuracy of registration algorithms important.	Sojka et al., 2021
Tractography (deterministic)	Reconstruction of white matter connections based on a preset (deterministic) direction at each voxel.	More specific results than with probabilistic tractography, higher efficiency. Lower re-test reliability than probabilistic models, susceptible to noise, unable to account for inherent uncertainty in fiber orientation estimates.	Ding et al., 2013; Hernando et al., 2015; Li et al., 2015b
Tractography (probabilistic)	Reconstruction of white matter tracts based on a stochastic spatial distribution estimates of fiber orientation.	Shows greater reproducibility than deterministic models, and accounts for the inherent uncertainty in fiber orientation estimates. Less specific than deterministic models, with greater spatial dispersion of reconstructed streamline (may lead to more false-positive connections).	Diez et al., 2021; Jungilligens et al., 2021; Sojka et al., 2021
Graph theory-based	Characterizes the structural connectome using nodes (cortical or subcortical regions-of-interest) and connectivity measurements (edges) derived from tractography.	Macroscopic representation of structural connectome, quantifying the relative structural connectivity between cortical regions. Results dependent on node segmentation, requiring assumptions to characterize white matter.	Diez et al., 2021; Ding et al., 2013; Sone et al., 2019
High angular resolution diffusion imaging (HARDI)	Measures diffusion signal along more gradient directions than conventional diffusion tensor imaging (DTI).	Can characterize both tensor metrics (e.g., fractional anisotropy) and tractography. Provides the orientation directions of multiple tracts found within a given voxel. Acquisition times are longer than traditional DTI sequences.	Goodman et al., 2020

The Abbreviations: FND, functional neurological disorder.

predictors of treatment response. Notably, neural circuit profiles predicting treatment response may or may not overlap with pathophysiological mechanisms.

Three studies examined functional activations and/or connectivity changes following treatment interventions (Espay et al., 2019; Faul et al., 2020; Vuilleumier et al., 2001). In one study, 15 patients with functional tremor underwent 12-weeks of CBT, as well as pre- and post-treatment participation in three tasks obtained during a single fMRI scan session: finger tapping, basic emotion processing (affectively-valenced face viewing) and intense emotion processing (International Affective Picture System images) (Espay et al., 2019). Here, relationships between baseline depression scores and post vs. pre-treatment activation patterns were investigated. Another fMRI study performed in 14 patients with FND-movt measured baseline and post-treatment activations using an emotional Go/No-Go task in the context of participating in a 5-day multidisciplinary motor retraining treatment program (Faul et al., 2020). This study adjusted for depression and anxiety scores, and also investigated how baseline fMRI profiles related to treatment response. A SPECT study conducted in 7 patients with functional sensorimotor deficits probed blood flow patterns while symptomatic and 2–4 months later once symptoms resolved (treated with supportive psychotherapy and physiotherapy) (Vuilleumier et al., 2001). Additionally, two studies in 22 outpatients with mixed FND investigated how baseline resting-state functional connectivity (Diez et al., 2019) and grey matter (Perez et al., 2018b) profiles related to prospectively collected 6-month clinical outcomes following individualized treatments (e.g., CBT, physical therapy); baseline depression and anxiety scores were used to contextualize findings. No prospective studies have evaluated relationships between white matter profiles and treatment outcomes. Real-time fMRI neurofeedback is another potential treatment to investigate in future FND research (Sukhodolsky et al., 2020).

## 12. Research Agenda

To summarize, FND neuroimaging research has grown over the past 20 years but continues to lag behind other prevalent neuropsychiatric disorders. Emerging themes include: i) brain dysfunctions in FND are distinct from feigning; ii) the pathophysiology of FND implicates multiple brain networks across functional and structural neuroimaging studies (e.g., abnormal salience/limbic-motor control and rTPJ-sensorimotor network interactions in fMRI studies); iii) linking neural mechanisms to etiological factors in FND is still in its early stages, as are biomarker studies of treatment response and prognosis. Task and resting-state fMRI have been the most widely used modalities to date, with few attempts to consider multimodal data. Replication has also been limited. Furthermore, while researchers have rapidly adopted “rule-in” examination signs and semiological features as core components of FND inclusion criteria, challenges remain regarding how (and if) to disentangle FND-related neural circuit profiles from other co-occurring mental and physical health symptoms. Likewise, questions regarding whether observed neuroimaging findings are disorder-specific, compensatory or linked to risk factors and confounds among other possibilities remain unanswered (Bègue et al., 2019).

To advance FND neuroimaging research over the next decade, we recommend the following research agenda. Note, this neuroimaging-focused research agenda is partially informed by recently published pathophysiology-focused research agenda formulations (Drane et al., 2020; Pick et al., 2019).

- **FND cohorts in neuroimaging studies require more detailed categorical and dimensional characterization across neurological, medical and psychiatric/psychological domains:** while emphasis on positive signs should remain a key inclusion criterion, future research should make concerted efforts to describe and quantify the range of functional neurological symptoms and other bodily symptoms experienced by individuals - most notably but not

limited to pain, fatigue, and cognitive complaints (Maggio et al., 2020; Nicholson et al., 2020). Additional work is also needed to operationalize and further validate rule-in signs for FND. Regarding FND phenotypes, the majority of studies to date focused on a single subtype (e.g., FND-seiz), while others further narrowed inclusion criteria to specific phenotypes within overarching categories (e.g., functional dystonia). While these efforts remain important, many patients with FND have mixed symptoms. Thus, greater clarity regarding the range of functional neurological symptoms present is needed in research cohorts; ongoing efforts by the FND Society to better operationalize FND diagnostic criteria will also aid cohort characterization. Similarly, consensus self-report and other measurements assessing additional distressing bodily symptoms if widely adopted would advance this effort and aid future data aggregation (see below) (Pick et al., 2020). The presence of functional somatic disorders (e.g., fibromyalgia) and other neurological conditions (e.g., traumatic brain injury) should also be documented. Similarly, life-time psychiatric symptomatology should be delineated using structured psychiatric interviews as well as dimensional psychopathological measurements; indices of adverse life experiences should be assessed across the lifespan. Medication use with known central nervous system effects should also be consistently detailed. Of note, caution should be taken to not overly emphasize the recruitment of “pure” forms of FND (those without neuropsychiatric comorbidities) – in part because the generalizability of such findings may be questionable. Furthermore, while we are recommending more robust cohort characterizations, we are not necessarily advocating for exhaustive assessments and recognize that investigators need to make tradeoffs depending on their study designs and research questions.

- **While healthy controls remain important, patient controls across neurological, psychiatric and medical diagnoses are needed to help delineate the specificity of observed FND findings.** Such patient controls could include individuals with chronic pain disorders, migraine, fibromyalgia, mild traumatic brain injury, major depression, generalized anxiety disorder, panic disorder, PTSD, dissociative disorders or mixed mood/anxiety psychiatric controls among other possibilities. Notably, some of these patient controls may have an overlapping pathophysiology with FND, observations that will nonetheless clarify disease mechanisms. Additionally, controls with similar symptoms driven by likely distinct neural mechanisms offer the opportunity to identify diagnostic biomarkers of FND; for example, comparing FND-seiz to epileptic seizures and comparing FND-movt to neurological disorders causing similar symptoms (e.g., primary dystonia). Lastly, it is beneficial to characterize healthy controls with the same measurements as those applied to patient groups.
- **Study designs should complement between-group approaches with relevant stratified between-group and within-group analyses.** Given that between-group (FND vs. controls) analyses are limited by the heterogeneity inherent to FND, stratified between-group analyses (FND-acute symptoms vs. FND-chronic symptoms; FND-prepubertal onset vs. FND-postpubertal onset) and within-group analyses provide important complementary information.
- **Longitudinal studies (naturalistic and pre/post treatment) are needed to investigate state vs. trait markers of FND pathophysiology, as well as to identify prognostic biomarkers and neural mechanisms of treatment response.** For example, while initial efforts have investigated structural and functional biomarkers of symptom severity cross-sectionally, it remains unclear how ‘responsive’ structural and functional brain profiles are to symptom fluctuations over time. Longitudinal studies may also help disentangle the importance of developmental trajectories and stress-diathesis model components in the pathophysiology of FND (Keynejad et al., 2019; Kozłowska, 2017).

- **Within-group designs investigating neural circuit profiles associated with symptom severity and illness duration may be particularly informative in elucidating the pathophysiology of FND.** As noted earlier, within-group designs can help account for co-occurring neuropsychiatric symptoms and improve statistical power; however, given that symptom severity and illness duration can also covary with other neuropsychiatric symptoms, secondary analyses should be performed with depression and anxiety scores (or similarly relevant factors) as covariates of noninterest.
- **In addition to mapping symptoms and relevant psychological constructs (e.g., agency, attentional biases, expectation/inference, alexithymia, dissociation, interoception, conversion, catastrophizing etc.) to neural circuit profiles, relationships between brain areas and other biological markers (neuroendocrine (e.g., stress and sex hormones), autonomic (e.g., heart rate variability and electrodermal skin responses), neuro-inflammatory, genetic and epigenetic factors) should be investigated.** Integrating a range of psychologically and biologically-relevant factors will help refine the understanding of links between what is observed in the brain and other bodily systems, as well as to overcome the dualism of separately studying psychological and neurobiological factors. Such multi-level measurement efforts will also help mitigate potential interpretation biases. Nonetheless, it is also important to note that while complex psychological functions can undoubtedly be further understood through neuroscience (Kandel, 2013), neuroimaging techniques – in their present form – may not be able to fully delineate some relevant processes such as free will (Hallett, 2016). Furthermore, composite biomarkers that include a range of psychobiologically-relevant variables may potentially exhibit greater explanatory power than a single measurement.
- **Multimodal (combined MRI, fMRI, DTI, EEG, and/or PET etc.) neuroimaging studies are encouraged to contextualize intrinsic structural and functional architectural profiles with task-related activation profiles.** This is analogous to collecting data from a resting echocardiography and exercise stress test to obtain a more complete picture of cardiac functioning. *In vivo* neurochemical (MRS) and nuclear medicine-based neurotransmitter binding studies would likely also add insights into the pathophysiology of FND. Similarly, EEG-fMRI studies can provide improved temporal resolution, while fMRI-TMS studies can interrogate discrete brain circuits to provide causal information.
- **Understanding how FND mechanisms and etiological factors relate to one another is important.** This should include efforts to contextualize roles for potential sex differences, developmental trajectories, stress coping, resilience, attachment, alexithymia and epigenetic / genetic factors. Contextualizing relationships across risk factors, including delineating moderators is another noteworthy research area.
- **Larger sample sizes are needed to comprehensively perform secondary and post-hoc analyses aimed at adjusting for potential confounding variables, as well as to assist in ensuring that findings are robust and replicable.** The future inclusion of test and replication cohorts in the same study would substantially increase the impact and clarity of neuroimaging findings.
- **To robustly address many of the above considerations, FND researchers should establish large-scale international data sharing initiatives.** One high impact consideration is to join the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium, an international effort by leaders worldwide to bring together clinical neuroscience researchers to understand pathological brain structure and function relationships, using MRI, DTI, fMRI & genetic data across patient populations (Thompson et al., 2020). ENIGMA's ethos is that the best return on research investments will come from combining data to achieve large samples necessary to detect modest imaging/gene effect sizes that we now know are the rule rather the exception for complex traits. A

particularly relevant consideration that we are actively exploring is to have FND researchers establish the FND working sub-group as part of the ENIGMA-Dissociation Working Group (Reinders, 2020). Dissociative symptoms are common in FND and its frequently co-occurring psychiatric conditions including PTSD, somatic symptom disorders, borderline personality disorder, anxiety disorders, and depersonalization/derealization disorder (Lyssenko et al., 2018). The ENIGMA-Dissociation Working Group is set up as an umbrella where individual subgroups investigate biomarkers of separate disorders involving dissociative symptoms. The amalgamation of the *within* disorder specific dissociation biomarkers from these separate segments will ultimately inform the study of biomarkers for pathological dissociation *across* disorders (Roydeva and Reinders, 2021). Additionally, disorder specific neural mechanisms could be investigated by performing large-scale between-group comparisons across FND and its co-occurring psychiatric conditions. Participation in the ENIGMA Consortium would also allow access to neuroimaging data across a range of other relevant disorders (e.g. traumatic brain injury) (Dennis et al., 2020).

### 13. Conclusions

Neuroimaging research in FND has steadily matured alongside substantial progress made in the diagnosis and treatment of this population. This article provides readers with an overview of the state of neuroimaging research in FND, emphasizing conceptual and methodological considerations. A research agenda to promote high impact neuroimaging-focused research questions is also outlined. Given complexity inherent to the pathophysiology of FND, there is an urgent need for large-scale collaborations to more definitely answer key mechanistic questions regarding FND. Advancing the pathophysiology of FND, in part through multimodal neuroimaging approaches, has important ramifications not only for FND but also for a more holistic conceptualization of mental and physical health more broadly.

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### Conflicts of Interest/Disclosures

D.L.P., honoraria from Harvard Medical School for continuing medical education lectures on FND and serves on the editorial board of *Epilepsy & Behavior*. A.A.A.P., Honoraria from Cobel Daruo,



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